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Calcium channel blockers for antipsychotic-induced tardive dyskinesia (Review)

Essali A, Soares-Weiser K, Bergman H, Adams CE

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Calcium channel blockers for antipsychotic-induced tardive dyskinesia.
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[Intervention Review]

Calcium channel blockers for antipsychotic-induced tardive dyskinesia

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ABSTRACT

Background

Schizophrenia and related disorders affect a sizable proportion of any population. Antipsychotic medications are the primary treatment for these disorders. Antipsychotic medications are associated with a variety of adverse effects including tardive dyskinesia. Dyskinesia is a disfiguring movement disorder of the orofacial region that can be tardive (having a slow or belated onset). Tardive dyskinesia is difficult to treat, despite experimentation with several treatments. Calcium channel blockers (diltiazem, nifedipine, nimodipine, verapamil, flunarizine) have been among these experimental treatments.

Objectives

To determine the effects of calcium channel blocker drugs (diltiazem, nifedipine, nimodipine, verapamil) for treatment of neuroleptic-induced tardive dyskinesia in people with schizophrenia, schizoaffective disorder or other chronic mental illnesses.

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (July 2015 and April 2017), inspected references of all identified studies for further trials and contacted authors of trials for additional information.

Selection criteria

We selected randomised controlled trials comparing calcium channel blockers with placebo, no intervention or any other intervention for people with both tardive dyskinesia and schizophrenia or serious mental illness who remained on their antipsychotic medication.

Data collection and analysis

We independently extracted data and estimated risk ratios of dichotomous data or mean differences (MD) of continuous data, with 95% confidence intervals (CI). We assumed that people who left the trials early had no improvement. We also created a 'Summary of findings' table using GRADE.

Main results

Previous versions of this review included no trials. From the 2015 search, we identified three cross-over trials that could be included. The 2017 search found no new studies relevant to this review. The included trials randomised 47 inpatients with chronic mental illnesses in the USA and China. Trials were published in the 1990s and were of short duration (six to 10 weeks). Overall, the risk of bias was unclear, mainly due to poor reporting; allocation concealment was not described, generation of the sequence was not explicit, studies were not clearly blinded, and attrition and outcome data were not fully reported. Findings were sparse, no study reported on the primary outcome 'no clinically important improvement in tardive dyskinesia symptoms,' but two small studies (37 participants) found no difference on the tardive dyskinesia symptoms scale Abnormal Involuntary Movement Scale (AIMS) scores between diltiazem or flunarizine and placebo

after three to four weeks' treatment (MD -0.71, 95% CI -2.68 to 1.26, very low quality evidence). Only one study randomising 20 participants reported on adverse events, and reported that there were no adverse events with flunarizine or with placebo (very low quality evidence). One study with 18 participants reported no events of deterioration in mental state with diltiazem or with placebo (very low quality evidence). No studies reported on acceptability of treatment or on social confidence, social inclusion, social networks or personalised quality of life outcomes designated important to patients.

Authors' conclusions

Available evidence from randomised controlled trials is extremely limited and very low quality, conclusions cannot be drawn. The effects of calcium channel blockers for antipsychotic-induced tardive dyskinesia are unknown. Their use is experimental and should only be given in the context of well-designed randomised trials.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers for antipsychotic-induced tardive dyskinesia

Review question

Are a group of medicines called calcium channel blockers (diltiazem, nifedipine, nimodipine, verapamil, flunarizine) useful for the treatment of an unpleasant side effect, tardive dyskinesia, in people with schizophrenia or similar mental health problems?

Background

People with schizophrenia often hear voices and see things (hallucinations) and have strange beliefs (delusions). These symptoms are usually treated with antipsychotic medicines. However, these drugs can have debilitating side effects. Tardive dyskinesia is an involuntary movement that causes the face, mouth, tongue and jaw to convulse, spasm and grimace. It is caused by long-term or high-dose of antipsychotic medicines, is difficult to treat and can be incurable. A group of medicines called calcium channel blockers (diltiazem, nifedipine, nimodipine, verapamil, flunarizine) have been used as experimental treatments for tardive dyskinesia.

Study characteristics

We searched for clinical trials (up to April 2017) using Cochrane Schizophrenia's specialised register of trials. The review includes three small, short trials published in the 1990s. The trials randomised 47 people with schizophrenia or other chronic mental illnesses who had also developed tardive dyskinesia because they were taking antipsychotic medicines. The treatments the participants received were the calcium channel blockers, flunarizine, nifedipine or diltiazem hydrochloride or placebo (dummy treatment).

Key results

A small set of very low quality data were available from three small and poorly reported trials. Currently, it is uncertain whether calcium channel blockers are helpful in the treatment of tardive dyskinesia that is caused by taking antipsychotic medicines. Therefore, the use of calcium channel blockers for this purpose remains experimental.

Quality of the evidence

Evidence was limited and small scale. It is not possible to recommend these drugs as a treatment for antipsychotic-induced tardive dyskinesia. To fully investigate whether calcium channel blockers have any positive effects, there would have to be more well-designed, conducted and reported clinical trials.

This plain language summary was adapted by the review authors from a summary originally written by Ben Gray, Senior Peer Researcher, McPin Foundation (mcpin.org/).

Summary of findings for the main comparison. Calcium channel blocking drugs for people with antipsychotic-induced tardive dyskinesia

Calcium channel blocking drugs for people with antipsychotic-induced tardive dyskinesia

Patient or population: people with antipsychotic-induced tardive dyskinesia

Settings: inpatients in China (1 study) and the Netherlands (1)

Intervention: calcium channel blocking drugs

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Calcium channel blocking drugs				
Tardive dyskinesia - not improved to a clinically important extent	No data from randomised trials for not improved to a clinically important extent. 2 RCTs found no significant difference on the continuous AIMS scale (MD -0.71, 95% CI -2.68 to 1.26, 2 RCTs, 37 participants, I^2 = 0%).			37 participants (2 studies)	⊕⊖⊖⊖ Very low [1,2,3]	-
Tardive dyskinesia - deterioration	No data from randomised trials.					
Adverse effects - any important adverse effects Follow-up: 4 weeks	See comment	See comment	Not estimable	20 participants (1 study)	⊕⊖⊖⊖ Very low [4,5]	1 study reported that there were no adverse events.
Adverse effects - important extrapyramidal adverse effects	No data from randomised trials.					
Mental state - deterioration Follow-up: 3 weeks	See comment	See comment	Not estimable	18 participants (1 study)	⊕⊖⊖⊖ Very low [5,6]	1 study reported that no participants deteriorated in mental state.

Acceptability of treatment - leaving the study early	No data from RCTs.
Social confidence, social inclusion, social networks or personalised quality of life measures - no clinically significant change	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AIMS: Abnormal Involuntary Movement Scale; **CI:** confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level for risk of bias: the included study did not adequately describe randomisation or blinding of outcome assessors, in one study, non-compliant participants (3/18) were excluded and replaced during the study.
[2] Downgraded two levels for imprecision: very small sample size, and wide 95% CIs that may have contained both appreciable benefit and no effect.
[3] Downgraded one level for indirectness: results on the continuous AIMS scale is not a direct measure of the outcome.
[4] Downgraded one level for risk of bias: the included study did not adequately describe allocation concealment or blinding of outcome assessors, and non-compliant participants (3/18) were excluded and replaced during the study.
[5] Downgraded two levels for imprecision: very small sample size, and effect could not be estimated due to no reported events.
[6] Downgraded one level for risk of bias: the included study did not adequately describe randomisation or blinding of outcome assessors.

BACKGROUND

Antipsychotic drugs are effective in treating and preventing relapse of schizophrenia and related psychoses (Schooler 1993). However, antipsychotic medications are associated with adverse effects that negatively affect quality of life and may lead to poor compliance; thus, ultimately, increasing the risk of relapse of people taking these medications (Barnes 1993). Some of the most troublesome adverse effects associated with antipsychotic medications involve movement disorders. The appearance of these disorders can be extremely disfiguring, can compound stigma and is associated with poor compliance to antipsychotic treatment (Barnes 1993; Tarsy 2011).

Description of the condition

Dyskinesia is a movement disorder characterised by involuntary, repetitive body movements that can be tardive (having a slow or belated onset). Tardive dyskinesia (TD) is characterised by repetitive, involuntary, purposeless movements, such as grimacing, tongue protrusion, lip smacking, puckering and pursing of the lips, and rapid eye blinking. Rapid movements of the extremities and impaired movements of the fingers may also occur. TD tends to be a chronic condition of insidious onset, the severity of which spontaneously fluctuates (APA 1992). Orofacial dyskinesia and trunk and limb dyskinesia may have different responses to treatment (APA 1992; Jeste 1982).

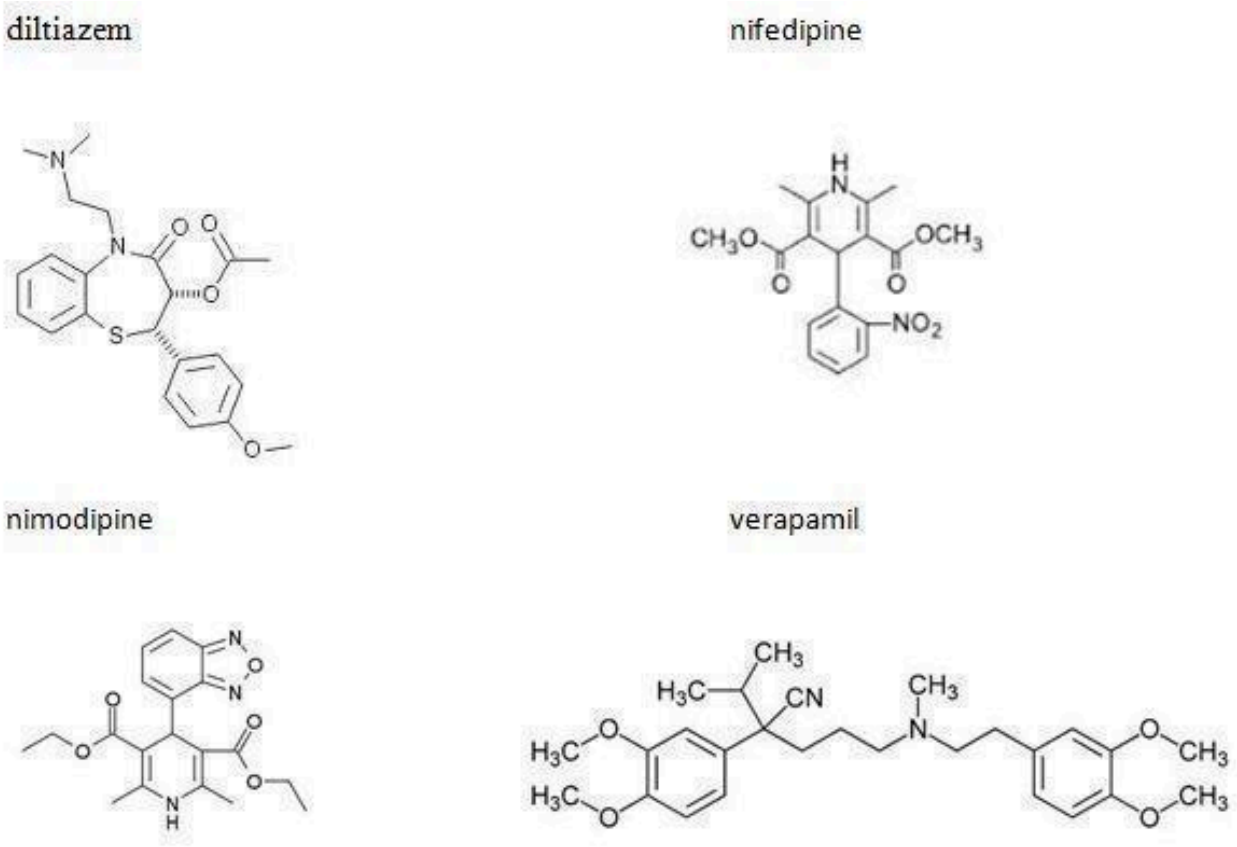
TD is often seen as an adverse effect of long-term or high-dose use of antipsychotic drugs. Within the first four years of using antipsychotic drugs, 18.5% of young adults and 31% of people over 55 years of age develop TD (Saltz 1991). It has been estimated that with each year of antipsychotic use, 5% of people will show signs of TD, (i.e. 5% after one year, 10% after two years and 15% after three years) with no clear upper limit (Jeste 1993). The incidence of TD varies with the type of antipsychotic drug. However, among newer atypical antipsychotics, only clozapine has been shown to have a lower risk of TD than older antipsychotic drugs (Fernandez 2003; Rauchverger 2007). TD may persist for months, years or even permanently after withdrawal of the drug, and it can result in considerable social and physical disability (Barnes 1993).

Description of the intervention

TD is difficult to treat. Several strategies have been advocated for treating the disorder, including changing an affected person's medication (Soares-Weiser 2006), or using many different treatments. A wide range of experimental treatments has been tried for TD; most remain unproven and this is one of a series of reviews in this area (Table 1).

Calcium channel blockers (diltiazem, nifedipine, nimodipine, verapamil, Figure 1) have important indications in cardiovascular disorders. Clinical trials of various calcium channel blockers in people with TD were stimulated by case reports of unexpected benefit. For instance, one study of four participants suggested that nifedipine may be effective in the treatment of antipsychotic-induced TD in people with schizophrenia (Suddath 1991). This suggestion was reinforced by similar low-quality studies (Cates 1993; Hendrickson 1994). However, when assessing the clinical efficacy of calcium channel blockers for TD, it should be remembered that these drugs could cause serious adverse effects, such as a decrease in blood pressure (hypotension), headaches, nausea, vomiting, depression and even an increase in signs of TD.

Figure 1. Calcium channel blockers.



How the intervention might work

Antipsychotic drugs are claimed to cause an imbalance in certain chemical receptor sites in the brain, specifically dopamine sites where there is overactivity, and cholinergic sites, where there is underactivity (Casey 1994; Cates 1993). Laboratory research suggests that TD may result primarily from antipsychotic-induced dopamine supersensitivity in the nigrostriatal pathway, with the D_2 dopamine receptor being most affected. Older 'typical' antipsychotics, which have greater affinity for the D_2 binding site, are associated with high risk for TD (Hoerger 2007).

Animal and human experiments have suggested that intracellular calcium ions inside the brain cells play a role in the regulation of dopamine and choline activity (Alexander 1979; Dubovsky 1988). Calcium channel blockers show intrinsic dopamine-blocking properties (Dubovsky 1988), and their effect on dopamine neurotransmission has been proposed as a biological basis for their potential therapeutic effect in TD (Snyder 1985; Tamminga 2002). However, calcium channel blockers are pharmacologically different. For instance, verapamil crosses the blood-brain barrier more readily than diltiazem or nifedipine and exhibits dopamine-antagonist properties (Wolf 1988). These differential effects stimulated clinical studies of the anti-tardive-dyskinesia effect of verapamil (Barrow 1986; Buck 1988). For example, in 13 treatment-refractory men with schizophrenia, TD improved three weeks after supplementing their chlorpromazine treatment with verapamil, and rebounded following verapamil discontinuation (Wolf 1988). One comparison between verapamil and diltiazem demonstrated a statistically significant reduction in TD ratings with verapamil but not with diltiazem (Adler 1988). Diltiazem was also ineffective in one double-blind, placebo-controlled, cross-over study (Falk 1988), and studies with nifedipine have likewise been disappointing. Moreover, verapamil itself showed no clinically or statistically significant changes in antipsychotic-induced TD in seven adults with mental retardation (Ricketts 1995). In addition, it is feasible that any improvement related to the use of calcium channel blockers for the treatment of TD may result from drug interactions with coprescribed antipsychotic medication (Stedman 1991). Such a feasibility argues against using calcium channel blockers for the treatment of antipsychotic-induced TD.

Why it is important to do this review

Schizophrenia and related disorders affect a sizable proportion of any population. Antipsychotic medications are the primary treatment for these disorders, and TD is a common adverse effect of this treatment. Despite experimenting with a wide variety of interventions (Table 1), there is still no satisfactory treatment for TD. Calcium channel blockers have been among the experimental interventions for TD.

Despite suggested potential benefits, the quality of evidence for the use of calcium channel blockers in the treatment of TD is yet to be determined. This review provides practitioners and patients

with the best available evidence for the effects of calcium channel blockers in antipsychotic-induced TD in people with schizophrenia and related disorders.

OBJECTIVES

To determine the effects of calcium channel blocker drugs (e.g. diltiazem, nifedipine, nimodipine, verapamil) for treatment of neuroleptic-induced tardive dyskinesia in people with schizophrenia, schizoaffective disorder or other chronic mental illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCT) that assessed the beneficial and harmful effects of calcium channel blockers in the treatment of antipsychotic-induced TD, with no restrictions on blinding, publication status or language.

Types of participants

People with schizophrenia, schizoaffective disorder or other chronic mental illnesses, diagnosed by any criteria, irrespective of gender, age or nationality who developed TD (diagnosed by any criteria) during antipsychotic treatment, and for whom the dose of antipsychotic medication had been stable for at least one month (the same applied for people free of antipsychotics).

Types of interventions

Calcium channel blockers (e.g.diltiazem, nifedipine, nimodipine, verapamil, flunarizine) at any dose compared with placebo or no intervention. For the 2015 update, a post hoc decision was made to also include studies evaluating calcium channel blockers compared with any other intervention for the treatment of TD.

Types of outcome measures

We planned to group all outcomes into time periods: short term (less than six weeks), medium term (between six weeks and six months) and long term (over six months). We defined clinical efficacy as an improvement in the symptoms of TD of more than 50%, on any scale, after at least six weeks of intervention.

Primary outcomes

1. **Tardive dyskinesia (TD)**
   a. No clinically important improvement in the symptoms of individuals, defined as more than 50% improvement on any TD scale - any time period.
2. **Adverse effects**
   a. No clinically significant extrapyramidal adverse effects - any time period.

Secondary outcomes

1. **Tardive dyskinesia (TD)**
   a. Any improvement in the symptoms of participants on any TD scale, as opposed to no improvement.
   b. Deterioration in the symptoms of participants, defined as any deleterious change on any TD scale.
   c. Mean change in severity of TD during the trial period.
   d. Mean difference (MD) in severity of TD at the end of the trial.
2. **General mental state changes**
   a. Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale.
   b. MD in severity of psychiatric symptoms at the end of the trial.
3. **Acceptability of the treatment**
   a. Acceptability of the intervention to the participant group as measured by numbers of people leaving the trial early.
4. **Adverse effects**
   a. Use of any anti-parkinsonism drugs.
   b. Mean score/change in extrapyramidal adverse effects.
   c. Acute dystonia.
5. **Other adverse effects, general and specific**
6. **Hospital and service utilisation outcomes**
   a. Hospital admission.
   b. Mean change in days in hospital.
   c. Improvement in hospital status (e.g. change from formal to informal admission status, use of seclusion, level of observation).
7. **Economic outcomes**
   a. Mean change in total cost of medical and mental health care.
   b. Total indirect and direct costs.
8. **Social confidence, social inclusion, social networks or personalised quality of life measures**
   a. No significant change in social confidence, social inclusion, social networks or personalised quality of life measures.
   b. Mean score/change in social confidence, social inclusion, social networks or personalised quality of life measures.
9. **Behaviour**
   a. Clinically significant agitation.
   b. Use of adjunctive medication for sedation.
   c. Aggression to self or others.
10. **Cognitive state**
   a. No clinically important change.
   b. No change, general and specific.

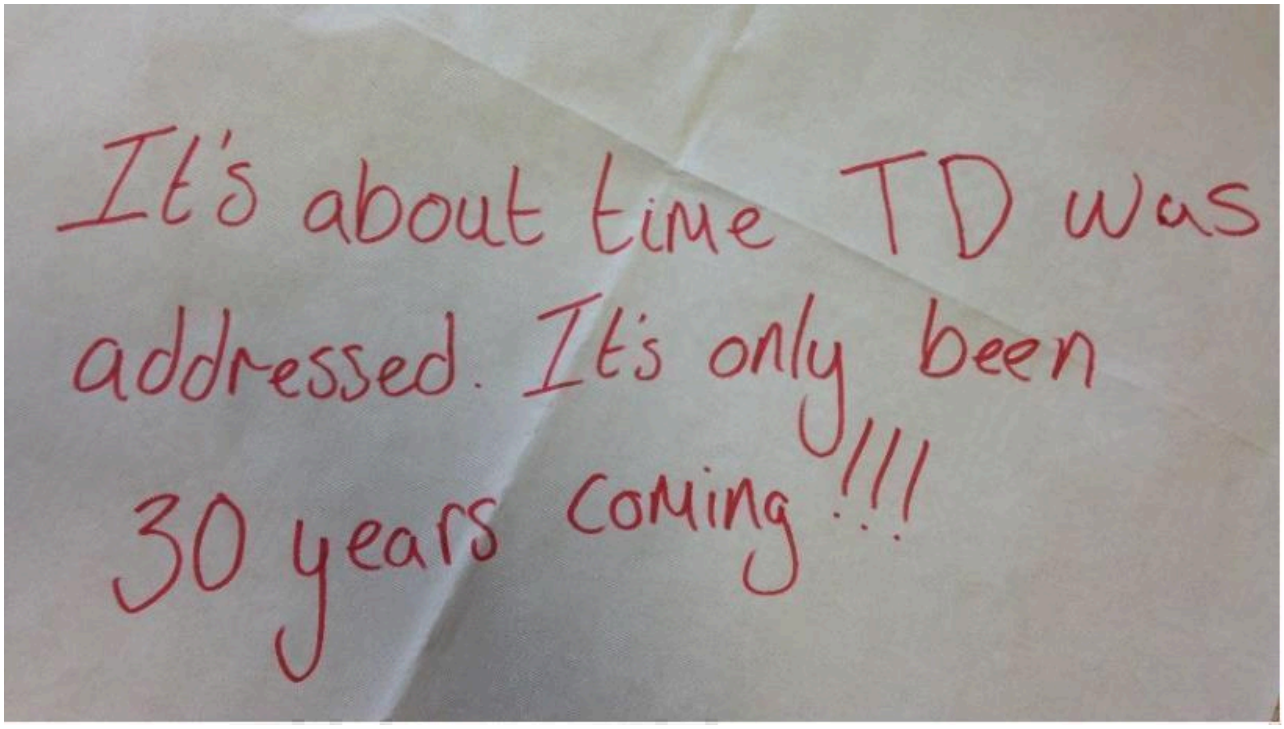
'Summary of findings' table

We used the GRADE approach to interpret findings (Schünemann 2008) and GRADEpro to import data from Review Manager 5 (RevMan 2014) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined and the sum of the available data on all outcomes we rated as important to patient care and decision making. This summary was used to guide our conclusions and recommendations. We selected the following main outcomes for inclusion in the 'Summary of findings' table.

1. Tardive dyskinesia.
   a. Not improved to a clinically important extent.
   b. Deteriorated.
2. Mental state.
   a. Deterioration.
3. Adverse effect.
   a. Any adverse event.
   b. Adverse effects: no clinically significant extrapyramidal adverse effects.
4. Acceptability of treatment.
   a. Leaving the study early.
5. Social confidence, social inclusion, social networks or personalised quality of life measures.*
   a. No significant change in social confidence, social inclusion, social networks or personalised quality of life measures for either recipients of care or carers.

* Outcome designated important to patients. We wished to add perspectives from people's personal experience with TD to the research agenda. A consultation with service users was planned where the previously published version of a review in the Cochrane TD series (Soares-Weiser 2011; Table 1) and a lay overview of the review gave the foundation for the discussions. The session was planned to provide time to reflect on current research on TD and consider gaps in knowledge. The report is not completed but we will add a link to it within this review but have added one figure showing service-user expression of frustration concerning this neglected area of research (Figure 2). Informed by the results of the consultation, for this review, we included outcomes important to service users to the Summary of findings for the main comparison.

Figure 2. Message from one of the participants of the public and patient involvement consultation of service user perspectives on tardive dyskinesia research.



Search methods for identification of studies

Electronic searches

The 2015 review update was carried out in parallel with updating eight other Cochrane TD reviews, see Table 1 for details. The search covered all nine TD reviews.

1. Cochrane Schizophrenia Group's Register

We searched Cochrane Schizophrenia Group's Study-Based Register of Trials on July 16, 2015 and April 26, 2017 using the following string:**Tardive Dyskinesia** in Healthcare Condition Field of Study.* In such a study-based register, searching the major concept retrieves all the synonym keywords and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics.The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group's Module). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

2. Details of previous electronic searches

See Appendix 1.

Searching other resources

1. Reference searching

We searched the reference lists of all included studies to identify more studies.

2. Personal contact

Where necessary, we contacted the first author of each included study for information regarding unpublished trials. We noted the outcome of this contact in the 'Characteristics of included studies' or 'Characteristics of excluded studies' tables.

Data collection and analysis

Selection of studies

For the 2015 and 2017 searches, two reviewers, RA and AG (see Acknowledgements) inspected all abstracts of studies identified to identify potentially relevant reports. We resolved disagreement by discussion, or where there was still doubt, we acquired the full article for further inspection. We acquired the full articles of relevant reports/abstracts meeting initial criteria for reassessment and carefully inspected for a final decision on inclusion (see Criteria for considering studies for this review). The review authors were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked a third review author (HB) for help and had it been impossible to decide, we planned to add these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Study selection was performed by KS-W and John McGrath for the initial version of this review (Soares 2001), by JR for the 2003 update (Soares-Weiser 2004), and by AE and HD (see Acknowledgements) for the 2011 update (Essali 2011).

Data extraction and management

1. Extraction

For the 2015 update, two review authors (HB and RA) extracted data from all included studies. We discussed any disagreement and documented decisions, requesting that a third review author (KSW) helped clarify issues and we documented these final decisions. We extracted data presented only in graphs and figures whenever possible, but included only if two review authors independently had the same result. We attempted to contact authors through an open-ended request to obtain missing information or for clarification whenever necessary. If studies were multi-centre, where possible, we extracted data relevant to each component centre separately.

2. Management

2.1. Forms

For the 2015 update, we extracted data on to simple forms. Extracted data are available here with a link to the original source PDF for each item (last accessed 1 August 2017).

2.2. Scale-derived data

We included continuous data from rating scales only if:

1. the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000); and
2. the measuring instrument was not written or modified by one of the trialists for that particular trial; and
3. the measuring instrument was either a self-report or completed by an independent rater or relative (not the therapist).

2.3. Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. However, calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. We decided primarily to use endpoint data and only use change data if the former were not available. We combined endpoint and change data in the analysis as we preferred to use MD rather than standardised mean differences (SMD) throughout (Higgins 2011; Chapter 9.4.5.2).

2.4. Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant data before inclusion.

Note: we entered data from studies of at least 200 participants in the analysis, because skewed data pose less of a problem in large studies. We also entered all relevant change data as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to determine whether data are skewed or not.

For endpoint data from studies with fewer than 200 participants:

1. when a scale started from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than 1, it strongly suggests a skew and we excluded these data. If this ratio was higher than 1 but below 2, there is suggestion of skew. We entered these data and tested whether their inclusion or exclusion change the results substantially. Finally, if the ratio was larger than 2, we included these data, because skew is less likely (Altman 1996; Higgins 2011).
2. if a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS) (Kay 1986)), which can have values from 30 to 210), we modified the calculation described above to take the scale starting point into account. In these cases, skew is present if 2 SD > (S - S_{min}), where S is the mean score and S_{min} is the minimum score.

2.5. Common measure

Where relevant, to facilitate comparison between trials, we converted variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6. Conversion of continuous to binary

Where possible, we converted continuous outcome measures to dichotomous data. This was done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS; Overall 1962) or PANSS (Kay 1986),

this can be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7. Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for calcium channel blockers. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we presented data where the left of the line indicated an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

Two review authors (RA and HB) independently assessed risk of bias within the included studies using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagreed, we made the final rating by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies to obtain further information. If non-concurrence occurred, we reported this.

We noted the level of risk of bias in the text of the review and in Figure 3; Figure 4; and Summary of findings for the main comparison.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

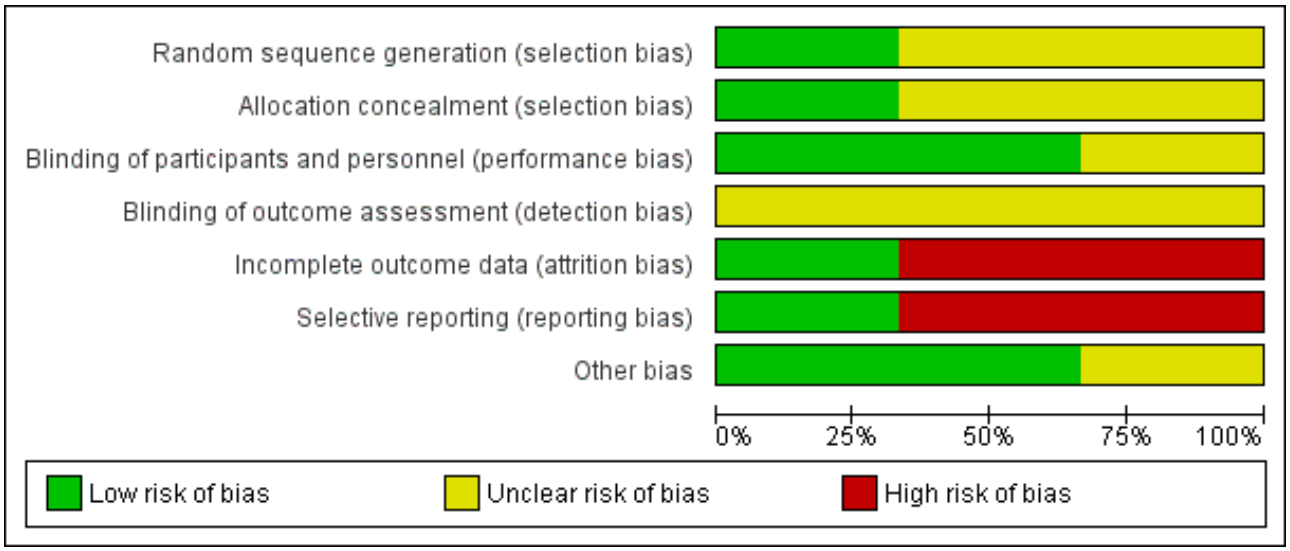
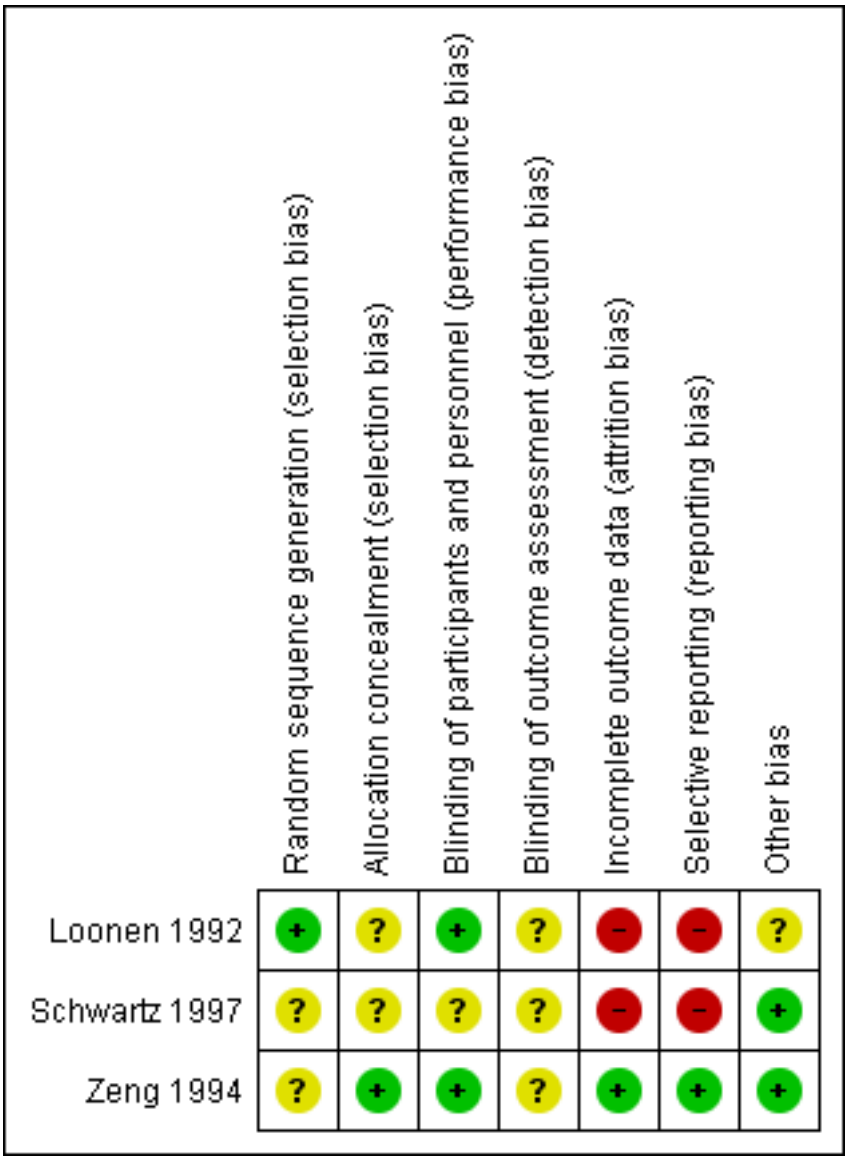


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

1. Binary data

For binary outcomes, we planned to calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios (ORs) and that ORs tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

For continuous outcomes, we planned to estimate MD between groups. We preferred not to calculate effect size measures SMD. However, had scales of very considerable similarity been used, we would have presumed there was a small difference in measurement, and we would have calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cross-over studies

This area of research commonly uses cross-over studies where one person is randomly allocated the treatment only to be crossed over to receive the comparison after a designated time. Often a period of drug free 'washout' is used between the interventions to try and ensure that no carry-over effects of the first intervention remain before commencing the second treatment. The statistical methods for including cross-over studies in meta-analyses have developed considerably (Curtin 2002a; Curtin 2002b; Curtin 2002c; Elbourne 2002).

However, there is a clinical problem. Antipsychotic-induced TD seems to result from the prolonged blockade of specific receptor sites in the brain resulting in changes (dopamine receptor hypersensitivity) that develop over long periods of time and are likely to be slow to reverse. Should an experimental intervention successfully begin the downgrading of the dopamine receptor sites,

it seems probable that this downgrading could take a long time to start and, once started, be equally slow to stop. Therefore, it seems entirely feasible that the drugs could have an effect even after they had been expelled from the body within the washout period. In addition, cross-over studies usually assume that the investigated condition should be stable (Elbourne 2002), and TD is not a stable condition. Consequently, we only used data of the first phase of cross-over studies in this review because of the nature of the condition under review.

2. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated, causing type I errors (Bland 1997; Gulliford 1999). We planned to deal with clustering in this review as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Section 16.3).

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, we would have presented the additional relevant treatment arms in comparisons. We would not have reproduced irrelevant additional treatment arms.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them in analyses. However, if more than 50% of participants in one arm of a study were lost, but the total loss was less than 50%, we addressed this within the 'Summary of findings' table by downgrading quality. We also downgraded quality within the 'Summary of findings' table should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). We assumed all participants leaving the study early had no improvement. We undertook a sensitivity analysis testing how prone the primary outcomes were to change by comparing data only from people who completed the study to that point to the ITT analysis using the above assumptions.

3. Continuous

3.1. Attrition

We reported and used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported.

3.2. Standard deviations

If SDs were not reported, we first tried to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either 'p' value or 't' value available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011): when only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011) present detailed formulae for estimating SDs from P values, t or F values, CI, ranges or other statistics. If these formulae did not apply, we calculated the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3. Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. Therefore, we did not exclude studies based on the statistical approach used. However, we preferred to use the more sophisticated approaches (e.g. MMRM or multiple-imputation) and only presented completer analyses if some type of ITT data were not available. Moreover, we addressed this issue in the item "incomplete outcome data" of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise and discussed in the text if they arose.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise and discussed in the text if they arose.

3. Statistical heterogeneity

3.1. Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2. Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 'P' value. The I^2 statistic provides

an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. 'P' value from Chi^2 test, or a CI for I^2 statistic). An I^2 statistic estimate of 50% or greater accompanied by a statistically significant Chi^2 statistic can be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Intervention*; Higgins 2011). We explored and discussed in the text potential reasons for substantial levels of heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in Section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We tried to locate protocols of included randomised trials. Where the protocol was available, we compared outcomes in the protocol and in the published report. Where the protocol was not available, we compared outcomes listed in the methods section of the trial report with the reported results.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not plan to use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we planned to seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which are often the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. Therefore, we intended to use the fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1. Calcium channel blocker

As calcium channel blockers may have differential effects on antipsychotic-induced TD, we performed a subgroup analysis to compare the effects of different calcium channel blockers. We proposed to undertake comparisons only for primary outcomes to minimise the risk of multiple comparisons.

1.2. Recent-onset tardive dyskinesia

We anticipated a subgroup analysis to test the hypothesis that the use of calcium channel blockers is most effective for people with recent-onset TD (less than five years). We had hoped to present data for this subgroup for the primary outcomes.

2. Investigation of heterogeneity

We would have reported inconsistency if it appeared high. First, we would have investigated whether data had been entered correctly. Second, if data had been entered correctly, we would have visually inspected the graph and removed outlying studies to see if homogeneity was restored. Should this have occurred with no more than 10% of the data being excluded, we would have presented the data. If not, we would have pooled the data and discussed the issues.

If unanticipated clinical or methodological heterogeneity had been obvious, we would have simply stated hypotheses regarding these for future reviews or updated versions of this review. We prespecified no characteristics of studies that may be associated with heterogeneity except quality of trial method. If no clear association could have been shown by sorting studies by the methodological quality, we would have performed a random-effects meta-analysis. Should another characteristic of the studies have been highlighted by the investigation of heterogeneity, perhaps some clinical heterogeneity not hitherto predicted or plausible causes of heterogeneity, we would have discussed these post hoc reasons and analysed and presented the data. However, should the heterogeneity have been substantially unaffected by use of random-effects meta-analysis and no other reasons for the heterogeneity have been clear, we would have presented the final data without a meta-analysis.

Sensitivity analysis

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. For the primary outcomes, we would have included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then we would have used all the data from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we would have compared the findings of the primary outcomes when we used our assumption compared only with completer data. If there had been a substantial difference, we would have reported results and discussed them but continued to employ our assumption.

3. Duration of follow-up

We would have undertaken a third sensitivity analysis to compare primary outcomes between short-term (less than six weeks), medium-term (between six weeks and six months) and long-term (over six months) trials.

RESULTS

Description of studies

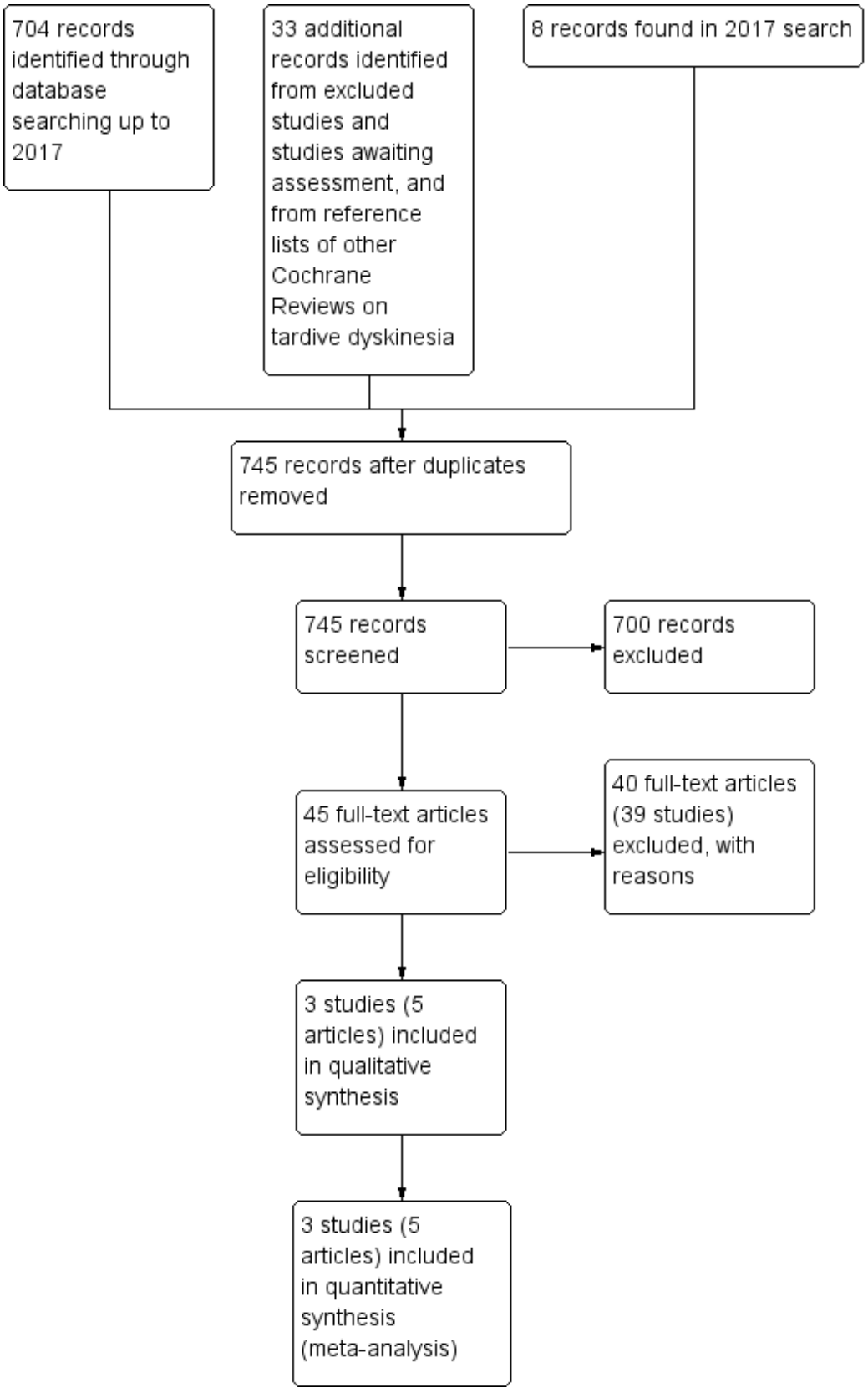
See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

The original searches identified thousands of citations. On inspection, very few of these studies were relevant to this review. The 2003 update search benefited from the legacy of work that had gone before and only found 15 studies not identified by the original search. Only nine of these were in any way relevant but all were excluded. The 2010 update search found no additional studies. The 2013 update search identified 38 studies, of which 16 had already been considered for this review. All the remaining 22 studies were excluded.

The searches up to 2017 retrieved 704 references for 344 studies, see Figure 5 for study flow diagram. The 2015 and 2017 update searches were part of an update of nine Cochrane reviews, see Table 1.

Figure 5. Study flow diagram (2015 and 2017 update search results only).



From the 2015 search, we excluded irrelevant references and screened titles and abstracts. We obtained full texts of 45 references (42 studies). One of these reports was a new study to this review in Chinese (Zeng 1994). Another two studies were previously excluded because all data were unusable (Loonen 1992; Schwartz 1997); however, we did find some useable data and could include them. Three studies are now included in this review (Loonen 1992; Schwartz 1997; Zeng 1994).

The 2017 search found 8 records (5 studies). Editorial base of Cochrane Schizophrenia screened these records and no new studies were relevant to this review. They could be relevant to another reviews in this series of TD reviews (see Table 1), and have been put into awaiting assessment of Soares-Weiser 2003.

Included studies

Overall the review now includes three studies with 47 participants published between 1992 and 1997.

1. Methods

All studies were stated to be randomised and double blind. For further details, see Allocation (selection bias) and Blinding (performance bias and detection bias) sections for further details.

2. Design

All three included studies presented a cross-over design with two periods. We had considered this as likely when embarking on the review and have used only the data from the first phase for the reasons outlined above in the Unit of analysis issues section.

3. Duration

All studies were of short duration (less than 10 weeks) and did not perform any long-term follow-ups. The study by Zeng 1994 employed a washout period of two weeks.

4. Participants

Participants, now totalling 47 people, were mostly men in their 50s, with diagnoses of various chronic psychiatric disorders, but mainly schizophrenia. All had antipsychotic-induced TD diagnosed using either Schooler and Kane's research diagnostic criteria or the Abnormal Involuntary Movement Scale (AIMS). The number of participants in the three included studies were 14 (Zeng 1994), 15 (Schwartz 1997), and 18 (Loonen 1992).

5. Setting

Trials were conducted in hospital. The studies themselves were from the USA (Schwartz 1997), China (Zeng 1994), and the Netherlands (Loonen 1992).

6. Interventions

6.1. Calcium channel blockers

6.1.1. Diltiazem hydrochloride

Loonen 1992 used diltiazem hydrochloride 60 mg, twice per day.

6.1.2. Nifedipine

Schwartz 1997 used nifedipine 60 mg per day.

6.1.3. Flunarizine

Zeng 1994 used flunarizine but did not specify the dose, reporting that participants took one capsule twice per day.

6.2. Comparison group

All studies used a placebo as a comparison group, with no further details given. None of the included studies compared calcium channel blockers to another active intervention.

Participants remained on schizophrenia treatment antipsychotic medication during the trials.

7. Outcomes

7.1. General

Some outcomes were presented in graphs, inexact P values of differences, or a statement of significant or non-significant difference. This made it impossible to acquire raw data for synthesis. Some continuous outcomes could not be extracted due to missing number of participants or missing means, SDs or SEs. All included studies used the LOCF strategy for the ITT analysis of dichotomous data.

7.2. Scales used to measure the tardive dyskinesia symptoms

We have shown details of the scales that provided usable data below. We have provided reasons for exclusions of data under 'Outcomes' in the Characteristics of included studies table.

7.2.1. Abnormal Involuntary Movement Scale

The AIMS is a 12-item scale consisting of a standardised examination followed by questions rating the orofacial, extremity and trunk movements, as well as three global measurements (Guy 1976). Each of these 10 items can be scored from 0 (none) to 4 (severe). Two additional items assess the dental status. The AIMS ranges from 0 to 40, with higher scores indicating greater severity.

7.3. Scales used to measure cognitive functioning

7.3.1. Dementia Rating Scale

The Dementia Rating Scale (DRS) is a five-item scale designed to assess level of cognitive functioning for people with brain dysfunction (Mattis 1988). The five scales are: attention, initiation-perseveration, construction, conceptualisation and memory.

Excluded studies

There were 39 excluded studies. Eleven studies were not randomised. We excluded 24 studies because participants had schizophrenia or other mental conditions but not TD. One excluded study did not report data separately for the included minority with TD (Suddath 1991). After many years of unsuccessful attempts to contact authors for further details, we have also excluded a further four randomised studies which reported no usable data (Leys 1988; Rzewuska 1995; Fay-McCarthy 1997a; Fay-McCarthy 1997b), or did not report data separately for the first phase before crossing over to the next treatment (Yamada 1996).

Studies awaiting assessment

We found no studies awaiting assessment.

Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

Refer to Figure 3 and Figure 4 for graphical overviews of the risk of bias in the included studies.

Allocation

Only Loonen 1992 provided explicit details about the randomisation sequence generation. The other two studies did not explain how allocation was achieved other than using the word "randomized." Zeng 1994 reported a centrally controlled allocation while the other two studies did not provide explicit details.

Blinding

Although all studies were conducted on a double-blind basis, Schwartz 1997 did not explicitly describe how this was undertaken. No study described the blinding of outcome assessors in detail or tested the blindness of raters, clinicians and trial participants.

Incomplete outcome data

Two studies were at high risk of attrition bias because they excluded participants who dropped out of the study from the analysis (Loonen 1992; Schwartz 1997). All participants in the study by Zeng 1994 completed the trial.

Selective reporting

The majority of data in this review originated from published reports. Expected outcomes (impact on TD symptoms) were reported by two of the three trials (Loonen 1992 and Zeng 1994) but only Zeng 1994 reported results of all outcomes listed in the methods section fully . Loonen 1992 and Schwartz 1997 did not fully report outcomes that were measured during the study and were rated at high risk of reporting bias. Attempts to contact authors of trials for additional data were unsuccessful.

Other potential sources of bias

All studies had small or very small sample sizes, and used a cross-over design. There was very little information reported on which to base further concerns regarding risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Calcium channel blocking drugs for people with antipsychotic-induced tardive dyskinesia

1. Comparison 1. Calcium channel blockers versus placebo

1.1. Tardive dyskinesia: AIMS endpoint score

We had chosen 'any improvement in TD symptoms of more than 50% on any TD scale - any time period' as a primary outcome. No data found in the included trials fit this exactly, so only endpoint scores of the AIMS were pooled.

TD symptoms were measured on the continuous AIMS scale (see Section 7.2 Scales used to measure the TD symptoms). There was no benefit of calcium channel blockers when compared to placebo after three to four weeks (2 RCTs, n = 37; MD -0.71, CI -2.68 to 1.26; very low quality evidence; I^2 = 0%; Analysis 1.1).

1.2. Adverse effects: any adverse effects (short term)

One study reported no adverse effects during the study period as a result of flunarizine or placebo (1 RCT, n = 20; RR not estimable; very low quality evidence; Analysis 1.2).

1.3. Mental state: deterioration (short term)

One trial found that no participant in diltiazem hydrochloride or placebo groups deteriorated during the study (1 RCT, n = 18; RR not estimable; very low quality evidence; Analysis 1.3).

1.4. Cognitive state: mean endpoint score (DRS, low = better)

One trial found no difference in cognitive function measured with the DRS (see Included studies) between nifedipine and placebo (1 RCT, n = 14; MD 2.50 CI -3.67 to 8.67; Analysis 1.4).

We did not identify any studies that reported on hospital and service utilisation outcomes, economic outcomes, social confidence, social inclusion, social networks, personalised quality of life, behaviour or that reported on leaving the study early during the first phase before crossing over to the next treatment in cross-over studies.

1.5. Subgroup analysis

1.5.1. Calcium channel blocker

We stratified the only outcome with data from more than one study by type of calcium channel blocker. There was no heterogeneity between flunarizine and diltiazem hydrochloride (I^2 = 0%, P = 0.82; Analysis 1.1).

1.5.2. Recent-onset tardive dyskinesia

It was not possible to evaluate whether participants with recent-onset TD responded differently to those with more established problems, since no trial reported data for groups with different durations of TD that could be extracted for separate analyses.

1.6. Heterogeneity

Data were homogeneous. We found no clinical, methodological or statistical heterogeneity as described in Assessment of heterogeneity.

1.7. Sensitivity analyses

1.7.1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. As all studies were stated to be randomised, we did not undertake this sensitivity analysis.

1.7.2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we intended to compare the findings when we used our assumption compared with completer data only. This sensitivity analysis could not be undertaken as there were no events for any binary data outcomes.

1.7.3. Duration of follow-up

We did not undertake a sensitivity analysis investigating duration of follow-up; included studies reported measures after very similar duration (three or four weeks).

2. Comparison 2. Calcium channel blockers versus any other active treatments

We found no trials reporting data on calcium channel blockers compared with other active treatments.

DISCUSSION

Summary of main results

1. The searches

This area of research does not seem to be active. The 2015 update identified additional data, but all trials predated the year 2000. The 2017 search identified no new data. This could be because of reasons such as less concern with TD, or less emergence of the problem in research-active communities because of more thoughtful use of antipsychotic drugs and loss of faith in calcium channel blockers as a potential treatment.

2. Few data

Calcium channel blockers are experimental in the treatment of TD (see Description of the intervention) and we did not expect to find much data. Only 47 people were included in this review. For this reason, it is likely that real, and important, effects have not been highlighted because of the necessarily wide CIs of the findings. Many outcomes were not measured (see Overall completeness and applicability of evidence), including several of our prestated outcome measures.

3. Comparison 1. Calcium channel blockers versus placebo

3.1. Tardive dyskinesia

We found no studies that reported on no clinically important improvement in TD symptoms or on deterioration of TD symptoms. Two RCTs found no significant difference on endpoint score on the continuous AIMS scale between diltiazem or flunarizine and placebo after three to four weeks treatment (2 RCTs, n = 37; MD -0.71, 95% CI -2.68 to 1.26; I^2 = 0%).

3.2. Adverse effects

One study with 20 participants reported that there were no adverse events in either study arm.

3.3. Mental state

One study with 18 participants reported that none of the participants deteriorated mentally in either study arm.

3.4. Leaving the study early

None of the included studies reported on leaving the study early during the first phase before crossing over to the next treatment.

3.5. Social confidence, social inclusion, social networks or personalised quality of life

This group of outcomes was selected as being of particular importance to patients for the 2015 review update following a service user consultation. We found no studies that reported on any of these outcomes.

Overall completeness and applicability of evidence

1. Completeness

Only three small studies with very few useable data were included, not sufficient to address the safety and efficacy of calcium channel blockers in the treatment of antipsychotic-induced TD in people with schizophrenia or other chronic mental illnesses. There was very little evidence on TD symptoms, and no evidence on adverse events; mental state; leaving the study early or on social confidence, social inclusion, social networks or personalised quality of life. If reporting had been better we may have been able to include more data from these studies, and we may have had some data to present from the excluded studies Leys 1988; Rzewuska 1995; Suddath 1991; and Yamada 1996.

2. Applicability

Trials were hospital based, and were on people who would be recognisable in everyday care. Calcium channel blockers are readily accessible and outcomes selected for the 'Summary of findings' table are understandable in terms of clinical practice. Should calcium channel blockers have had important effects, the findings may well have been applicable.

Quality of the evidence

We cannot draw any robust conclusions regarding the effects, good or bad, of calcium channel blockers on TD; only three cross-over studies of short duration with 47 participants could be included, which severely limited the quality of the evidence. The largest trial randomised only 18 people. A trial of this size is unable to detect subtle, yet important differences due to an intervention with any confidence. In order to detect a 20% difference between groups, probably about 150 people are needed in each arm of the study (alpha 0.05, beta 0.8). Overall, the quality of reporting of these trials was poor (see Figure 3). Allocation concealment was not described, generation of the sequence was not explicit, studies were not clearly blinded, attrition was not clearly reported for the first cross-over phase and data were not fully reported. The small sample size and the poor reporting means that we have very little confidence in the effect estimates, and the true effects are likely to be substantially different from the estimates of the effects.

Potential biases in the review process

1. Missing studies

Every effort was made to identify relevant trials. However, these studies were all small and it is likely that we have failed to identify other studies of limited power. It is likely that such studies would also not be in favour of the intervention group. If they had been so, it is more likely that they would have been published in accessible literature. However, we do not think it likely that we have failed to identify large relevant studies.

2. Introducing bias

We did have foreknowledge of the past work in this area and could have been biased in how data were managed or reported. We welcome comments or criticisms. For the 2015 review update, a new author joined the team. We re-examined excluded references and found data that could be included (see this link for exact source of data in the PDFs; last accessed 1 August 2017). We also updated the 'Summary of findings' table outcomes following a patient consultation.

Agreements and disagreements with other studies or reviews

The only other relevant quantitative review we know of is the previous Cochrane Review versions (Essali 2011; Soares 2001; Soares-Weiser 2004). This update identified three studies to include (as discussed in Results of the search and Potential biases in the review process), but the very sparse and low-quality evidence lead to no substantial change in the conclusions. Findings from other similar reviews (see Table 1) suggest that TD, rather than these interventions, is no longer a focus of research activity. However, studies evaluating treatments for TD are of importance to people with the problem (Figure 2) and have long been ignored.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with tardive dyskinesia

Based on currently available data, this systematic review provides no conclusions about the use of calcium channel blockers for the treatment of antipsychotic-induced tardive dyskinesia (TD) - except that they are purely experimental treatments. People with TD should only take such experimental interventions, with their potential to do harm, within the context of well-designed randomised controlled trials.

2. For clinicians

In the absence of reliable evidence, clinicians prescribing calcium channel blockers for people with TD must balance the possible benefits against the potential adverse effects of the treatment. Calcium channel blockers lower people's blood pressure and may even cause symptoms of TD to increase. These drugs should only be used in a situation where their effects are closely monitored, that is, within randomised trials designed to inform practice.

3. For policy makers

There is no indication that calcium channel blockers should be introduced as part of routine treatment policy for people with TD. However, policy makers could specify that such experimental treatments only be used within the context of a trial.

4. For funders of research

Calcium channel blockers for TD would not seem to be the first set of compounds to choose to investigate within randomised studies. However, if a funding agency was intent on supporting such research, stipulation of the design outlined under 'Further trials' in Implications for research and in Table 2 and reporting issues would seem prudent.

Implications for research

1. Reporting

Two out of three of the included studies in this review preceded the CONSORT statement (Begg 1996; Moher 2001), so the quality of data reporting might be expected to be lower than at present. Future studies should rigorously apply the standards of reporting as outlined in CONSORT and also make all data freely available.

2. Further reviews

As is usual with systematic reviews, several studies were identified that could be added into existing reviews or suggested comparisons for new reviews of the future. These are listed in Table 3.

3. Further trials

Because calcium channel blockers have dopamine-blocking properties, this group of drugs could be implicated in the *appearance* of TD. This makes the necessity of further trials debatable. However, if further randomised trials are being planned, then inclusion of the following design elements would be helpful.

1. Use of a parallel-group, placebo-controlled design. This has benefits over cross-over studies. Trialists find it difficult to identify people with both TD and schizophrenia to participate in trials. Randomised cross-over design is used in the hope of improving the power of the study to find outcomes of interest. This design initially asks participants to be randomised to one of the experimental interventions, and then, at a prespecified time, to be crossed over to the other treatment. Conditions with a more stable time course than TD are better suited for cross-over studies (Fleiss 1984). Further difficulties are related to the carry-over effect. Unless cross-over studies include a mid-study washout period (where the person is free of treatment before starting the next arm of the study), any effect of the first intervention may continue into the second half placebo arm of the trial (the 'carry-over effect'). Also, carry-over may involve the regrowth or retreat of neuroreceptors. This slow rebalancing, if started, could continue long after all traces of intervention drugs are gone, so physiological half life of the experimental treatment may not be the only variable to consider when thinking through the issues of carry-over. TD is also an unstable condition and people with TD may not remain compliant with medication. All these factors make the arguments for not using cross-over methodology strong, despite the initial attraction (Armitage 1991; Fleiss 1984; Pocock 1983).
2. Trials which extend for at least six weeks.
3. Sample size which is sufficiently large to avoid false conclusions about effectiveness of intervention.

A suggested design is outlined in Table 2.

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The Methods section of this review used text from the Cochrane Schizophrenia Group's generic text for methods sections. This has

been written over a period of years to ensure consistency and clarity. We fully acknowledge use of this text which we have adapted for relevance to this particular review.

We would like to acknowledge Hany Deirawan who searched literature, selected trials, rewrote sections of the report and updated methods for the 2011 and 2013 updates.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Loonen 1992

Methods	Allocation: "random permuted block," allocation not described. Blindness: "double-blind to placebo tablets which looked identically." Duration: 6 weeks (3 weeks then crossed over for another 3 weeks). Design: cross-over. Setting: inpatients, the Netherlands. Raters: not reported.
Participants	Diagnosis: DSM-III-R psychiatric diagnoses (schizophrenia, personality and development disorders) and clinical diagnosis of TD. Duration of TD: > 6 months. n = 18*. Sex: 11 women, 6 men (among completers). Age: mean (SD): 57.2 (9.30) years; range 37-69 years.
Interventions	1. Diltiazem hydrochloride: dose 60 mg 4 times daily (n = 9). 2. Placebo (n = 9). All stable on antipsychotics for ≥ 3 weeks before entry and during the trial. Concomitant medication: all stable for ≥ 3 weeks before entry and during the trial: anticholinergics (n = 9), benzodiazepines (n = 2), anticonvulsants (n = 2) and diuretics (n = 2).
Outcomes	TD symptoms: AIMS. Mental state: deterioration (CGI).
Notes	Sponsorship source: not reported. *2 participants were non-compliant and were replaced.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants who entered the study randomly allocated to treatment group 1 or 2 by random permuted block technique with a block size of 2. Random number generator method to select random permuted blocks not reported, but likely computer generated.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias)	Low risk	"double-blind to placebo tablets which looked identically;" "The double-blind code was not broken until the last patient had terminated."

Loonen 1992 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details of blinding of assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not intention-to-treat. "Eighteen patients with TD entered the study. During the study, three subjects terminated prematurely. Two of them showed an obvious lack of compliance unrelated to trial medication; these subjects were replaced. One patient developed atrial fibrillation, which required digitalization. When the double-blind code of this patient was broken, it appeared that the atrial fibrillation had started during the placebo period. Thus, the number of subjects who completed the study was 17." Unclear when the non-compliant participants were replaced (period 1 or 2) and which group they were randomised to.
Selective reporting (reporting bias)	High risk	Full trial report available with all outcomes reported but most outcomes not reported for the first period before cross-over.
Other bias	Unclear risk	Unable to assess baseline differences - characteristics were reported per participant but not per group, therefore, unclear if there were confounding variables that may have led to bias.

Schwartz 1997

Methods	Allocation: "random assignment." Blindness: "double-blind." Duration: 8 weeks (4 weeks then crossed over for another 4 weeks). Design: cross-over. Setting: not described, USA. Raters: not described.
Participants	Diagnosis: schizophrenia or schizoaffective disorder (DSM-lll-R). Research criteria for TD: "moderate" abnormal involuntary movements in ≥ 1 body areas or at least a rating of "mild" movements in ≥ 2 body areas on the AIMS. Duration of TD: not reported. n = 15. Sex: 14 men, 1 woman. Age: mean 45.7 years; range 36-58 years.
Interventions	1. Nifedipine: 60 mg/day for 4 weeks (n = 9). 2. Placebo (n = 5). All stable on antipsychotics, captopril mean dose 1405 mg (range 150-6250 mg) for ≥ 1 month before entry and during the trial. Concomitant medication: not reported.
Outcomes	Cognitive changes (DRS) (digitised and extracted from figure).

Schwartz 1997 *(Continued)*

	Unable to use: Mental state: BPRS, SANS (data not fully reported). Adverse effects: AIMS, SAS, BAS, Chouinard and Ross-Chouinard Scale (data not fully reported).
Notes	Sponsorship source: support from the National Institute of Mental Health (to last author).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"random assignment;" further details were not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment details not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind;" further details were not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double-blind;" further details were not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not intention-to-treat. "The data for one patient from one test phase was missing; therefore, there were 14 patients included in the analysis of data."
Selective reporting (reporting bias)	High risk	Several outcomes not fully reported.
Other bias	Low risk	"statistical comparisons showed that patients in the two drug orders did not differ from each other in terms of age, severity of initial psychiatric symptoms or abnormal movements, dose of antipsychotic medication, or duration of illness." The study seemed free of other sources of bias.

Zeng 1994

Methods	Allocation: "random," allocation properly described. Blindness: described and adequate. Duration: 10 weeks (4 weeks, 2-week washout then crossed over for another 4 weeks). Design: cross-over. Setting: Institute of Mental Health Institute of Jining, Shan dong, China. Raters: not described.
Participants	Diagnosis: people with schizophrenia and antipsychotic-induced TD; AIMS ≥ 5; normal physical and laboratory examinations. Duration of TD: mean (SD) 5.9 (3.4) years.

Zeng 1994 *(Continued)*

	n = 14. Sex: 11 male, 3 female. Age: mean (SD) 31 (9) years. Stable antipsychotic dose for ≥ 5 months before study commencement. All participants received stable nerve blockade (such as phenothiazines, haloperidol, sulpiride). Other concomitant medication not reported.
Interventions	1. Flunarizine: at first phase, 1 capsule, twice per day for 4 weeks (n = 10). 2. Placebo: at first phase, 1 capsule, twice per day for 4 weeks (n = 10).
Outcomes	TD symptoms: AIMS. Adverse events: any adverse events.
Notes	Sponsorship source: not reported. Chinese language publication; assessed and data extracted by Sai Zhao.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"cross over randomised trial;" further details not reported.
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled central allocation: "the interventions were coded as intervention A or B by the researcher in the pharmacy."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind study, the interventions were coded as intervention A or B by the researcher in pharmacy;" "Participants and personnel did not know the allocation result. The two drugs contained in capsules with the same appearance." Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants competed study.
Selective reporting (reporting bias)	Low risk	Authors reported all measured outcomes.
Other bias	Low risk	No further concerns.

AIMS: Abnormal Involuntary Movement Scale; BAS: ; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; DRS: Dementia Rating Scale; DSM-III-R: Diagnostic & Statistical Manual of Mental Disorders - 3rd Edition Revised; n: number of participants; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson-Angus Extrapyramidal Signs Scale; SD: standard deviation; TD: tardive dyskinesia.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adler 1988	Allocation: not described as randomised or double blind, only raters were described as blinded.
Alexander 1978	Allocation: not randomised.
Alexander 1979	Allocation: not randomised.
Athanassenas 1983	Allocation: not randomised.
Bisol 2008	Allocation: randomised. Participants: people with chronic DSM-IV-defined schizophrenia, not with TD. Interventions: flunarizine compared with haloperidol.
Brambilla 1992	Allocation: not randomised.
Carman 1979	Allocation: "double blind." Participants: people with psychosis, not with TD. Interventions: dihydrotachysterol.
Dose 1991	Allocation: randomised. Participants: people with schizophrenia, not with TD. Interventions: carbamazepine vs valproate vs beclamide vs placebo.
Duncan 1990	Allocation: not randomised, cohort study.
Egan 2013	Allocation: randomised. Participants: people with schizophrenia, acutely ill, not with TD. Interventions: MK-8998 vs olanzapine vs placebo.
Ehrenreich 2007	Allocation: randomised. Participants: men with chronic schizophrenia, not with TD. Interventions: recombinant human erythropoietin vs placebo.
Falk 1988	Allocation: not randomised, case report.
Fay-McCarthy 1997a	Allocation: "random order." Participants: people with schizophrenia, not with TD. Interventions: nifedipine vs placebo. Outcomes: no usable data.
Fay-McCarthy 1997b	Allocation: unclear, cross-over study. Participants: people with schizophrenia, not with TD. Interventions: nifedipine vs placebo. Outcomes: no usable data (authors contacted, no reply).

Study	Reason for exclusion
Grebb 1986	Allocation: not randomised, case report.
Huang 2004	Allocation: randomised. Participants: people with senility with first-episode schizophrenia, not with TD. Interventions: perphenazine vs perphenazine + nimodipine.
Janicak 1998	Allocation: randomised. Participants: people with mania, not with TD. Interventions: verapamil vs placebo.
Krupitsky 1999	Allocation: randomised. Participants: healthy people, not with TD. Interventions: nimodipine vs ketamine vs placebo.
Lara 2009	Allocation: randomised. Participants: people with schizophrenia, not with TD. Interventions: flunarizine vs haloperidol.
Leys 1988	Allocation: randomised. Participants: TD over 6 months + psychosis (n = 3), vomiting (n = 1), bipolar disorder (n = 1), behavioural disturbances related to Alzheimer's disease (n = 1). Interventions: diltiazem hydrochloride vs placebo. Outcomes: no usable outcome data reported. Contacted study author for data and no reply was received. Consequently, we excluded this over 25-years-old study.
Liebman 2010	Allocation: randomised. Participants: people with schizophrenia, not with TD. Interventions: tiagabine (Gabitril) vs placebo added to their antipsychotic regimen.
NCT00425815	Allocation: randomised. Participants: people with schizophrenia, not with TD. Interventions: org 24448 (ampakine) vs placebo.
NCT00469664	Allocation: randomised. Participants: people with schizophrenia, not with TD. Interventions: guanfacine vs placebo.
NCT00512070	Allocation: randomised. Participants: people with schizophrenia, not with TD. Interventions: melatonin vs placebo.
Nechifor 2004	Allocation: not randomised.

Study	Reason for exclusion
Pickar 1987	Allocation: "double blind." Participants: people with schizophrenia, not with TD. Interventions: verapamil vs placebo.
Popov 2008	Allocation: not clear. Participants: people with schizophrenia treated with haloperidol, not with TD. Intervention: nifedipine or no treatment to prevent the emergence of extrapyramidal adverse effects.
Price 1986	Allocation: "double blind," unclear if randomised, cross-over. Participants: people with schizophrenia, not with TD. Interventions: verapamil vs haloperidol.
Ricketts 1995	Allocation: randomised. Participants: people with mental retardation, not people with schizophrenia and TD.
Ross 1987	Allocation: not randomised, case study
Rzewuska 1995	Allocation: "double blind," not stated as randomised. Participants: people with schizophrenia (ICD-10 diagnostic criteria) and postantipsychotic TD (n = 32). Outcomes: BPRS, CGI, TDRS, adverse effects (physical examination, routine blood tests, ECG). Assessment time: 0, 7, 14 and 28 days. Notes: no usable data. BPRS and TDRS results reported as % reduction. We were unable to identify up-to-date contact details of author for this 22-year-old study.
Suddath 1991	Allocation: randomised, cross-over trial. Participants: 4/10 people with TD. Interventions: nifedipine vs placebo. Outcomes: impossible to extract data relevant to people with TD. Contacted authors for more information but no reply received and study is > 20 years old.
Wang 1995	Allocation: "double blind." Participants: people with sinus tachycardia induced by antipsychotic drugs, not with TD. Interventions: propranolol vs verapamil.
Wei 1995	Allocation: "double blind." Participants: people with sinus tachycardia induced by antipsychotic drugs, not with TD. Interventions: propranolol vs verapamil.
Wei 2008	Allocation: not described. Participants: people with schizophrenia, not with TD.

Study	Reason for exclusion
	Interventions: nimodipine + sulpiride for negative symptoms of schizophrenia.
Yamada 1996	Allocation: "randomly assigned," cross-over trial. Participants: people with schizophrenia. Interventions: nilvadipine vs placebo. Outcomes: no separated data available for first half of study prior to cross-over. Contacted authors for more information but no reply received and the study is > 10 years old.
Yaryura 1968	Allocation: not described, unlikely to be randomised. Participants: people with schizophrenia, not with TD. Interventions: intravenous calcium gluconate vs sterile water.

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders - 4th Edition; ECG: electrocardiogram; ICD-10: International Statistical Classification of Diseases - 10th Revision; TD: tardive dyskinesia; TDRS: Tardive Dyskinesia Rating Scale.

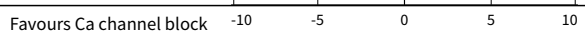
DATA AND ANALYSES

Comparison 1. Calcium channel blockers versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: AIMS endpoint score (low = better)	2	37	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-2.68, 1.26]
1.1 Diltiazem vs placebo - short term	1	17	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-5.55, 5.29]
1.2 Flunarizine vs placebo - short term	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.91, 1.31]
2 Adverse effects: any adverse effects (short term)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Mental state: deterioration (short-term)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Cognitive state: mean endpoint score (DRS, low = better, short term)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

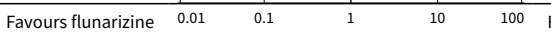
Analysis 1.1. Comparison 1 Calcium channel blockers versus placebo, Outcome 1 Tardive dyskinesia: AIMS endpoint score (low = better).

Study or subgroup	Calcium channel blocker N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 Diltiazem vs placebo - short term							
Loonen 1992	8	7.3 (5.3)	9	7.4 (6.1)		13.21%	-0.13[-5.55,5.29]
Subtotal ***	**8**		**9**			**13.21%**	**-0.13[-5.55,5.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.05(P=0.96)							
1.1.2 Flunarizine vs placebo - short term							
Zeng 1994	10	5.7 (2)	10	6.5 (2.8)		86.79%	-0.8[-2.91,1.31]
Subtotal ***	**10**		**10**			**86.79%**	**-0.8[-2.91,1.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.74(P=0.46)							
Total ***	**18**		**19**			**100%**	**-0.71[-2.68,1.26]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%							
Test for overall effect: Z=0.71(P=0.48)							
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%							



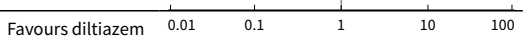
Analysis 1.2. Comparison 1 Calcium channel blockers versus placebo, Outcome 2 Adverse effects: any adverse effects (short term).

Study or subgroup	Flunarizine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Zeng 1994	0/10	0/10			Not estimable



Analysis 1.3. Comparison 1 Calcium channel blockers versus placebo, Outcome 3 Mental state: deterioration (short-term).

Study or subgroup	Diltiazem n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Loonen 1992	0/9	0/9		Not estimable



Analysis 1.4. Comparison 1 Calcium channel blockers versus placebo, Outcome 4 Cognitive state: mean endpoint score (DRS, low = better, short term).

Study or subgroup	Nifedipine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Schwartz 1997	9	34 (3.6)	5	31.5 (6.5)		0%	2.5[-3.67,8.67]

ADDITIONAL TABLES

Table 1. Other Cochrane Reviews in the tardive dyskinesia series

Focus of review	Reference
Benzodiazepines for neuroleptic-induced tardive dyskinesia	Bhoopathi 2006; update to be published
Cholinergic medication for neuroleptic-induced tardive dyskinesia	Tammenmaa 2002; update to be published
Anticholinergic medication for neuroleptic-induced tardive dyskinesia	Soares 2000; update to be published
Catecholaminergic drugs for neuroleptic-induced tardive dyskinesia	El-Sayeh 2006; update to be published
Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia	Alabed 2011; update to be published
Miscellaneous treatments* for neuroleptic-induced tardive dyskinesia	Soares-Weiser 2003; update to be published
Neuroleptic reduction or cessation (or both) and neuroleptics	Soares-Weiser 2006; update to be published
Non-neuroleptic catecholaminergic drugs	El-Sayeh 2006; update to be published
Vitamin E for neuroleptic-induced tardive dyskinesia	McGrath 2001; update to be published

* Includes botulinum toxin, endorphin, essential fatty acid, EX11582A, ganglioside, insulin, lithium, naloxone, oestrogen, periactin, phenylalanine, paracetamol, stepholidine, tryptophan, neurosurgery and electroconvulsive therapy.

Table 2. Suggested design of study

Methods	Allocation: randomised, fully explicit description of methods of randomisation and allocation concealment. Blinding: double, tested. Setting: anywhere. Duration: at least 6 weeks.
Participants	Diagnosis: schizophrenia, with tardive dyskinesia (clinical diagnoses, operational for random sample). n = 300.[1] Age: adults. Sex: both.
Interventions	1. Calcium channel blocker (n = 150). 2. Placebo (n = 150).
Outcomes	Tardive dyskinesia: any clinically important improvement in tardive dyskinesia, any improvement, deterioration[2]. Adverse effects: no clinically significant extrapyramidal adverse effects - any time period[3], use of any antiparkinsonism drugs, other important adverse events. Leaving the study early.

Table 2. Suggested design of study *(Continued)*

	Service outcomes: admitted, number of admissions, length of hospitalisation, contacts with psychiatric services. Compliance with drugs. Economic evaluations: cost-effectiveness, cost-benefit. General state: relapse, frequency, and intensity of minor and major exacerbations. Social confidence, social inclusion, social networks or personalised quality of life: binary measure. Distress among relatives: binary measure. Burden on family: binary measure.
Notes	[1] Powered to be able to identify a difference of about 20% between groups for primary outcome with adequate degree of certainty. [2] This simple measure can be used to target specific aspects of functioning, symptoms or attitudes. [3] Primary outcome. The same applies to the measure of primary outcome as for diagnosis. Not everyone may need to have operational criteria applied if clinical impression is proved to be accurate.

n: number of participants.

Table 3. Reviews suggested by excluded studies[1]

Study tag	Intervention			Suggested review
	#1	#2	#3	
Yaryura 1968	Calcium gluconate (iv)	Placebo	-	Mineral supplements for schizophrenia.
Dose 1991	Carbamazepine		Sodium valproate	Carbamazepine for schizophrenia; Valproate for schizophrenia.
Carman 1979	Dihydrotachysterol		-	Vitamin D for schizophrenia.
Bisol 2008, Lara 2009	Flunarizine	Haloperidol	-	Calcium channel blockers for schizophrenia.
NCT00469664	Guanfacine	Placebo	-	Central nervous system stimulants for schizophrenia.
NCT00512070	Melatonin		-	Melatonin for schizophrenia.
Egan 2013	MK-8998		Olanzapine	Calcium channel blockers for schizophrenia; Olanzapine versus placebo for schizophrenia
Popov 2008	Nifedipine		-	Calcium channel blockers for schizophrenia.
Fay-McCarthy 1997a			-	
Fay-McCarthy 1997b			-	

Table 3. Reviews suggested by excluded studies[1] *(Continued)*

Wei 2008	Nimodipine + sulpiride		-	
NCT00425815	Farampator (Org 24448)		-	Glutamate receptor stimulants for schizophrenia.
Huang 2004	Nimodipine + perphenazine	Perphenazine	-	Calcium channel blockers for schizophrenia.
Ehrenreich 2007	Recombinant human erythropoietin	Placebo	-	Glycoprotein hormones for schizophrenia.
Liebman 2010	Tiagabine		-	Anticonvulsants, miscellaneous for schizophrenia.
Price 1986	Verapamil	Haloperidol	-	Calcium channel blockers for schizophrenia.
Pickar 1987		Placebo	-	
Wang 1995; Wei 1995[2]		Propranolol	-	

[1] Sorted by Intervention #1; omitting studies not relevant to people with schizophrenia.
[2] People with sinus tachycardia induced by antipsychotic drugs, not with tardive dyskinesia - all other participants in studies were people with schizophrenia but not with tardive dyskinesia.

APPENDICES

Appendix 1. Previous searches

1. Update of 2010

We searched the Cochrane Schizophrenia Group Trials Register in May 2010 using the phrase: [((*calcium* or *diltiazem* or *nifedipine* or *nimodipine* or *verapamil*) in title or (*calcium* or *diltiazem* or *nifedipine* or *nimodipine* or *verapamil*) in title, abstract or Index terms of REFERENCE) or (*calcium* or *diltiazem* or *nifedipine* or *nimodipine* or *verapamil*) in intervention of STUDY]. The Schizophrenia Group's trials register is based on regular searches of BIOSIS Inside, CENTRAL, CINAHL, Embase, MEDLINE and PsycINFO; the handsearching of relevant journals and conference proceedings, and searches of several key grey literature sources. A full description is given in the Group's Module.

2. 2003 update

The Cochrane Schizophrenia Group's trials register was searched using the phrase: [((calcium* or diltiazem* or nifedipine* or nimodipine* or verapamil*) in title or (*calcium* or *diltiazem* or *nifedipine* or *nimodipine* or *verapamil) in title, abstract or Index terms of REFERENCE) or (calcium* or diltiazem* or nifedipine* or nimodipine* or verapamil*) in intervention of STUDY]. The Schizophrenia Group's trials register is based on regular searches of BIOSIS Inside, CENTRAL, CINAHL, Embase, MEDLINE and PsycINFO; the hand searching of relevant journals and conference proceedings, and searches of several key grey literature sources. A full description is given in the Group's module.

3. Earlier searches

3.1 Electronic searching

Relevant randomised trials were identified by searching several electronic databases (Biological Abstracts, the Cochrane Library, Cochrane Schizophrenia Group's Register of trials, Embase, LILACS, MEDLINE, PsycLIT and SCISEARCH).

The Cochrane Schizophrenia Group's Register was searched using the phrase: [calcium* or diltiazem or nifedipine or nimodipine or verapamil or (#42 = 304 or 33)]; #42 is the 'intervention' field within the Cochrane Schizophrenia Group's Register and 304 and 33 are codes for the calcium channel blocking drugs within that field.

Biological Abstracts (January 1982 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase: [and ((tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*))]. This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil].

Embase (January 1980 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase: [and ((tardive dyskinesia in thesaurus - subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive or dyskines*) or (movement* or disorder*) or (abnormal or movement* or disorder*))]. This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil].

LILACS (January 1982 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase: [and ((tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus))]. This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil].

MEDLINE (January 1966 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase: [and ((movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and (psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]. This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil].

PsycLIT (January 1974 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase: [and ((explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]. This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil].

SCISEARCH - Science Citation Index database. Reports of articles that have cited these studies were inspected in order to identify further trials.

3.2 Reference searching

The references of all identified studies were also inspected for more studies.

3.3 Personal contact

The first author of each included study was contacted for information regarding unpublished trials.

Appendix 2. Assessment of methodological quality in previous versions of this review

The methodological quality of the trials included in previous versions of this review would have been assessed using the criteria described in the *Cochrane Collaboration Handbook* (Clarke 2003) and the Jadad Scale (Jadad 1996). The former is based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment (Schulz 1995) and is defined as below.

A. Low risk of bias (adequate allocation concealment).
B. Moderate risk of bias (unclear allocation concealment).
C. High risk of bias (inadequate allocation concealment).

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale is made up of three items.

1. Was the study described as randomised?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Each item receives one point if the answer is positive. In addition, a point can be deducted or added according to the description of either the randomisation or the blinding/masking procedures.

For the purpose of the analysis in this review, trials would have been included if they had met criteria A or B of the *Cochrane Collaboration Handbook*. Additionally, a cut-off of two points on the Jadad scale would have been used to check the assessment made by the *Cochrane Collaboration Handbook* criteria if any studies had met the inclusion criteria.

Appendix 3. Methods section of 2004 version of this review

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. Where a trial was described as 'double-blind' but it was implied that the study was randomised and the demographic details of each group were similar, it was included. Quasi-randomised studies, such as those allocated by using alternate days of the week, were excluded.

Types of participants

People with schizophrenia or schizoaffective disorder or any other serious mental illness, diagnosed by any criteria, irrespective of gender, age or nationality who fulfilled the following criteria.

1. Required the use of neuroleptic drugs for more than three months.
2. Developed tardive dyskinesia (diagnosed by any criteria) during neuroleptic treatment.
3. For whom the dose of neuroleptic medication had been stable for one month or more.

Types of interventions

1. Calcium channel blockers (diltiazem, nifedipine, nimodipine, verapamil): any dose.
2. Placebo or no intervention.

Types of outcome measures

Clinical efficacy was defined as an improvement in the symptoms of tardive dyskinesia of more than 50%, on any scale, after at least six weeks of intervention.

Outcomes of interest were classified in three categories.

1. Tardive dyskinesia changes
1.1 Any improvement in the symptoms of participants of more than 50% on any tardive dyskinesia scale*.
1.2 Any improvement in the symptoms of participants on any tardive dyskinesia scale, as opposed to no improvement.
1.3 Deterioration in the symptoms of participants, defined as any deleterious change on any tardive dyskinesia scale.
1.4 Mean change in severity of tardive dyskinesia during the trial period.
1.5 Mean difference in severity of tardive dyskinesia at the end of the trial.

2. General mental state changes
2.1 Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale.
2.2 Mean difference in severity of psychiatric symptoms at the end of the trial.

3. Acceptability of the treatment
3.1 Acceptability of the intervention to the participant group as measured by numbers of people dropping out during the trial.

4. Adverse effects
4.1 No clinically significant extrapyramidal adverse effects*.
4.2 Use of any antiparkinsonism drugs.
4.3 Mean score/change in extrapyramidal adverse effects.
4.4 Acute dystonia.

5. Other adverse effects, general and specific

6. Hospital and service utilisation outcomes
6.1 Hospital admission.
6.2 Mean change in days in hospital.
6.3 Improvement in hospital status (e.g. change from formal to informal admission status, use of seclusion, level of observation).

7. Economic outcomes
7.1 Mean change in total cost of medical and mental health care.
7.2 Total indirect and direct costs.

8. Quality of life/satisfaction with care for either recipients of care or carers.
8.1 No significant change in quality of life/satisfaction.
8.2 Mean score/change in quality of life/satisfaction.

9. Behaviour
9.1 Clinically significant agitation.
9.2 Use of adjunctive medication for sedation.
9.3 Aggression to self or others.

10. Cognitive response
10.1 No clinically important change.
10.2 No change, general and specific.

* Primary outcome

All outcomes were grouped into time periods - short term (less than six weeks), medium term (between six weeks and six months) and long term (over six months).

Search methods for identification of studies

1. Electronic searching for update
1.1 Cochrane Schizophrenia Group's trials register (September 2003) was searched using the phrase:

[((calcium* or diltiazem* or nifedipine* or nimodipine* or verapamil*) in title or (*calcium* or *diltiazem* or *nifedipine* or *nimodipine* or *verapamil) in title, abstract or Index terms of REFERENCE) or (calcium* or diltiazem* or nifedipine* or nimodipine* or verapamil*) in intervention of STUDY]

The Schizophrenia Group's trials register is based on regular searches of BIOSIS Inside, CENTRAL, CINAHL, Embase, MEDLINE and PsycINFO; the hand searching of relevant journals and conference proceedings, and searches of several key grey literature sources. A full description is given in the Group's module.

2. Details of previous electronic search

2.1. Electronic searching

Relevant randomised trials were identified by searching several electronic databases (Biological Abstracts, Cochrane Library, Cochrane Schizophrenia Group's Register of trials, Embase, LILACS, MEDLINE, PsycLIT and SCISEARCH).

2.2. Cochrane Schizophrenia Group's Register was searched using the phrase:

[calcium* or diltiazem or nifedipine or nimodipine or verapamil or (#42 = 304 or 33)]

#42 is the 'intervention' field within the Cochrane Schizophrenia Group's Register and 304 and 33 are codes for the calcium channel blocking drugs within that field.

2.3. Biological Abstracts (January 1982 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil]

2.4. Embase (January 1980 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((tardive dyskinesia in thesaurus -subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive or dyskines*) or (movement* or disorder*) or (abnormal or movement* or disorder*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil]

2.5. LILACS (January 1982 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil]

2.6. MEDLINE (January 1966 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and (psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil]

2.7. PsycLIT (January 1974 to November 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and ((explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [calcium* or diltiazem or nifedipine or nimodipine or verapamil]

2.8. SCISEARCH - Science Citation Index

Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that have cited these studies were inspected in order to identify further trials.

3. Reference searching

The references of all identified studies were also inspected for more studies.

4. Personal contact

The first author of each included study was contacted for information regarding unpublished trials.

Data collection and analysis [For definitions of terms used in this, and other sections, please refer to the Glossary.]

1. Selection of studies

KS-W and John McGrath, working independently, inspected each reference identified by the search to see if the study was likely to be relevant. The full article was obtained for articles that could possibly have been relevant or to provide clarification in cases of disagreement between the two reviewers. These articles were then inspected, again independently, to assess their relevance to this review. Where resolving disagreement by discussion was not possible, the article was added to those awaiting assessment and the authors of the study were contacted for clarification. For the 2003 update, JR independently inspected citations from the update search (2003) and identified relevant abstracts. Full reports of the abstracts meeting the review criteria were obtained and inspected by JR.

2. Assessment of methodological quality

The methodological quality of the trials included in this review would have been assessed using the criteria described in the Cochrane Handbook (Clarke 2003) and the Jadad Scale (Jadad 1996). The former is based on the evidence of a strong relationship between the potential for bias in the results and the allocation concealment (Schulz 1995) and is defined as below:

A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (unclear allocation concealment)
C. High risk of bias (inadequate allocation concealment)

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale is made up of three items:

1. Was the study described as randomised?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and dropouts?

Each item receives one point if the answer is positive. In addition, a point can be deducted or added according to the description of either the randomisation or the blinding/masking procedures.

For the purpose of the analysis in this review, trials would have been included if they had met criteria A or B of the Handbook. Additionally, a cut-off of two points on the Jadad scale would have been used to check the assessment made by the Handbook criteria if any studies had met the inclusion criteria.

3. Data management

3.1. Data extraction

KS and JR would have independently extracted the data of the trials included; where further clarification was needed, the authors of trials would have been contacted to provide missing data.

3.2. Assumption for those lost to follow up

Data would have been excluded from studies where more than 50% of participants in any group were lost to follow up. Regarding the outcomes of 'aggression', 'self harm' and 'harm to others', as they are major risks of non-treated acute psychotic illness, we would have considered 5% of the people leaving the study early to have had a negative outcome. For other events, in studies with less than 50% dropout rate, people leaving early would have been considered to have had the negative outcome, except for the event of death.

If fewer than 95% of people had been reported at two hour follow up, a sensitivity analysis would have been undertaken for primary outcomes, to see if inclusion of these studies made a substantive change in estimate of effects. If they did, then data would have been presented separately. The impact of including studies with high attrition rates after the two-hour period of follow up (25-50%) would also have been analysed in a sensitivity analysis. If inclusion of data from this latter group had resulted in a substantive change in estimate of effects of the primary outcomes, their data would not have been added to trials with less attrition, but presented separately.

3.3. Cross-over studies

This area of research commonly uses cross over studies where one person is randomly allocated the treatment only to be crossed over to receive the comparison after a certain designated time period. Often a period of drug free 'washout' is used between the interventions to try and ensure that no carry-over effects of the first intervention remain before commencing the second treatment. Since the initial publication of this review, the statistical methods for including cross-over studies in meta-analyses have developed considerably (Curtin 2002a, Curtin 2002b, Curtin 2002c, Elbourne 2002). For the condition of tardive dyskinesia, however, the reviewers remain against use of these data within the review (see Discussion 2. Cross-over studies).

4. Data analysis

4.1. Dichotomous - yes/no - data

For binary outcomes a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI) would have been calculated. The number needed to treat or harm statistic (NNT, NNH), and its 95% confidence interval (CI), would also have been calculated. If heterogeneity had been found (see section 5) a random-effects model would have been used.

4.2. Continuous data

4.2.1. Skewed data: continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, the following standards would have been applied to all data before inclusion: (a) standard deviations and means are reported in the paper or are obtainable from the authors; (b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); (c) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above in (b) should be modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied to them. When continuous data are presented on a scale which includes a possibility of negative values (such as change on a scale), there is no way of telling whether data are non-normally distributed (skewed) or not. It is thus preferable to use scale end point data, which typically cannot have negative values. If end point data was not available, the reviewers would have used change data, but these would not have been subject to a meta-analysis, and would have been reported in the 'Additional data' tables.

4.2.2. Summary statistic: for continuous outcomes a weighted mean difference (WMD) between groups would have been estimated. If heterogeneity had been found (see section 5) a random-effects model would have been used.

4.2.3. Valid scales: continuous data from rating scales would have been included only if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000) and the instrument was either a self report or completed by an independent rater or relative (not the therapist).

4.2.4. Endpoint versus change data

Where possible, endpoint data would have been presented and if both endpoint and change data had been available for the same outcomes, only the former would have been reported in this review.

4.2.5. Cluster trials: studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a

'unit of analysis' error (Divine 1992) - whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated - causing type I errors (Bland 1997, Gulliford 1999). Secondly, RevMan does not currently support meta-analytic pooling of clustered dichotomous data, even when these are correctly analysed by the authors of primary studies, since the 'design effect' (a statistical correction for clustering) cannot be incorporated.

If clustering had not been accounted for in primary studies, we would have presented the data in a table, with a (*) symbol - to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to seek intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). If clustering had been incorporated into the analysis of primary studies, we would also have presented these data as if from a non-cluster randomised study, but adjusted for the clustering effect. We have sought statistical advice from the MRC Biostatistics Unit, Cambridge, UK. Dr Julian Higgins has advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect = 1+(m-1)*ICC]. If the ICC was not be reported we would have assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

5. Test for inconsistency

Firstly, consideration of all the included studies within any comparison would have been undertaken to estimate clinical heterogeneity. Then visual inspection of graphs would have been used to investigate the possibility of statistical heterogeneity. This would have been supplemented employing, primarily, the I-squared statistic. This provides an estimate of the percentage of inconsistency thought to be due to chance. Where the I-squared estimate included 75%, this would have been interpreted as evidence of high levels of heterogeneity (Higgins 2003). Data would then have been re-analysed using a random-effects model to see if this made a substantial difference. If it did, and results became more consistent, falling below 75% in the estimate, the studies would have been added to the main body trials. If using the random-effects model did not make a difference and inconsistency remained high, data would not have been summated, but presented separately and reasons for heterogeneity investigated.

6. Addressing publication bias

Data from all identified and selected trials would have been entered into a funnel graph (trial effect versus trial size) in an attempt to investigate the likelihood of overt publication bias.

7. Sensitivity analyses

We intended to undertake an analysis of the primary outcomes comparing the results when completer-only data were used with analyses on an intention-to-treat basis.

WHAT'S NEW

Date	Event	Description
18 October 2017	New citation required but conclusions have not changed	New data added does not change previous conclusions.
26 April 2017	New search has been performed	Update search run 26 April, 2017. Eight records found and assessed by editorial base at Cochrane Schizophrenia, none of the records found were relevant to this review. The records were all added to Studies awaiting classification of Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (see also Results of the search).
16 May 2016	Amended	Title changed from 'Calcium channel blockers for neuroleptic-induced tardive dyskinesia'. Three new included trials added (Loonen 1992; Schwartz 1997; Zeng 1994), analyses and text updated, outcomes list updated due to patient consultation, Summary of findings table updated, conclusions not substantially changed.
16 July 2015	Amended	Update search run July 2015.

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 3, 1997

Date	Event	Description
17 October 2013	New search has been performed	Update search run August 2013.
1 May 2013	Amended	Contact details updated.
17 October 2012	Amended	Contact details updated.
31 August 2011	New citation required but conclusions have not changed	Substantial update but no change to conclusions
14 April 2010	New search has been performed	New search undertaken, no new studies, substantially reformatted and findings clarified.
11 November 2009	Amended	Contact details updated.
25 April 2008	Amended	Converted to new review format.
22 October 2003	New citation required and conclusions have changed	Substantive amendment
3 October 2003	Amended	Minor revision
3 September 2003	New search has been performed	New studies found and included or excluded
21 November 2000	Amended	Conclusions changed
30 July 1999	Amended	Reformatted
27 August 1997	New search has been performed	New search.
2 September 1996	Amended	Review first published

CONTRIBUTIONS OF AUTHORS

AE (2011 and 2013 update): selected trials updated the methods, searched literature, helped rewrite the report.

KSW: protocol development, searching, data extraction, data assimilation, report writing.

HB (2015 update): trial selection, data extraction and assimilation, 'Summary of findings' table, report writing.

CEA (2011 and 2015 updates): report writing.

DECLARATIONS OF INTEREST

AE: none known.

KSW is the Deputy Editor-in-Chief for Cochrane and Cochrane Innovations. When the NHIR HTA programme grant was awarded that included to update this review, Karla was the Managing Director of Enhance Reviews Ltd.

HB worked for Enhance Reviews Ltd during preparation of this review and was paid for her contribution to this review. Enhance Reviews Ltd is a private company that performs systematic reviews of literature. HB works for Cochrane Response, an evidence consultancy linked to Cochrane that take commissions from healthcare guideline developers and policy makers.

CEA: none known.

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  Salary support for Hanna Bergman.
  Support for patient involvement consultation.
  Support for traceable data database.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have substantively reworded the protocol of this review. We consider that this rewording represents an improvement in clarity but, also, that it did not substantively change our procedures by which we undertook the review. For the record, the methods section of the previous version of this review is reproduced in Appendix 3.

For the 2015 update, the biggest changes to affect the review methods were to:

1. change the title from 'Calcium channel blockers for neuroleptic-induced tardive dyskinesia' to 'Calcium channel blockers for antipsychotic-induced tardive dyskinesia;' and
2. update list of outcomes following consultation with consumers.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*adverse effects]; Calcium Channel Blockers [*therapeutic use]; Diltiazem [*therapeutic use]; Dyskinesia, Drug-Induced [*drug therapy]; Flunarizine [*therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [drug therapy]

MeSH check words

Humans